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N-Tosyl-3-Azacyclohexyne. Synthesis and Chemistry of a Strained Cyclic Ynamide

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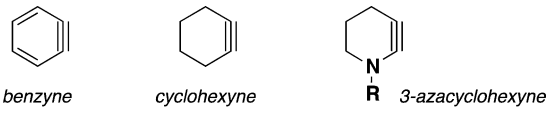
Supporting Information

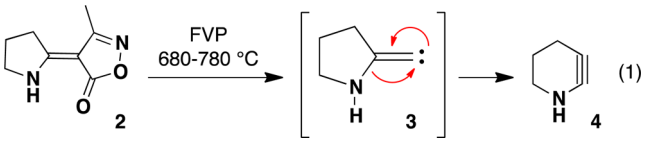
ABSTRACT: The first synthesis of a strained six-membered cyclic ynamide is described. *N*-Tosyl-3-azacyclohexyne is generated via fluoride-promoted 1,2 elimination under conditions that allow trapping of the strained heterocyclic alkyne in a variety of addition, insertion, and [2 + 2], [3 + 2], and [4 + 2] cycloaddition reactions.

The role of *o*-benzyne as the key intermediate in the reaction of chlorobenzene with KNH_2 was established through a series of groundbreaking experiments reported by J. D. Roberts et al. in 1953.[1] Today arynes [2] and hetarynes[3] rank among the most extensively studied reactive intermediates in organic chemistry. The electronic structure of these highly strained alkynes continues to attract great interest, and these remarkable species also have found an important place as building blocks in organic synthesis. [4] Cyclohexynes, on the other hand, are considerably less stable than benzynes, and to date these more exotic species have found very limited use in synthesis.[5,6] Even less attention has been focused on *heterocyclic* variants of cyclohexyne, and the application of these species in synthesis has not previously been explored. Our interest in the application of ynamides as synthetic building blocks[7,8] led us to consider whether the preparation of strained *cyclic* ynamides such as **1** might be feasible and whether such species might engage in transformations with utility for the construction of complex molecules. Herein we report the first synthesis of *N*-tosyl-3-azacyclohexyne (**1**) as well as its participation in highly regioselective transformations leading to a diverse range of heterocyclic compounds.



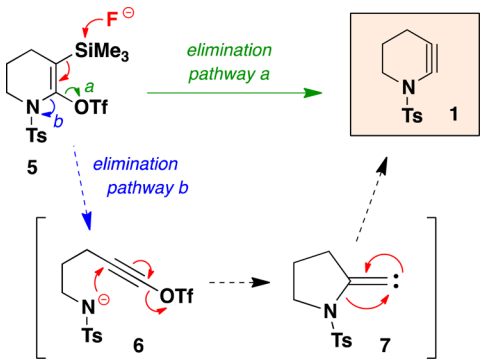
1 R = Ts

To our knowledge, only a single report of the generation of an azacyclohexyne has appeared previously. In 1988, Wentrup et al. reported that flash vacuum pyrolysis of isoxazolone **2** provides access to azacyclohexyne **4** which was identified through the use of low-temperature IR spectroscopy.[9] Decomposition of the unstable heterocyclic alkyne was observed to take place upon warming above −150 °C. The formation of azacyclohexyne in this reaction is believed to proceed via the rearrangement of the intermediate carbene **3** (eq 1).



For our initial studies on the chemistry of azacyclohexynes, we focused our attention on the *N*-tosyl derivative **1** and targeted the cyclic enamide **5** as a potential intermediate for its synthesis (Scheme 1).[10] Several considerations motivated our choice of **5** as an attractive precursor to the strained cyclic alkyne. First, several alternate routes could be envisioned for the preparation of **5** beginning with readily available derivatives of δ-valerolactam. Exposure of **5** to the action of fluoride ion was then expected to provide access to the azacyclohexyne under mild conditions that would be compatible with the presence of a wide range of interesting reaction partners capable of trapping the strained alkyne. Note that the elimination process proposed for the generation of **1** from **5** (Scheme 1, pathway a) constitutes a variant of the well established Kobayashi method for the preparation of arynes from *o*-(trialkylsilyl)aryl triflates.[11] It is relevant to note that 1,2-eliminations of this type have previously been employed for the generation of cyclohexyne[6c,f] as well as 1,2,3-cyclohexatriene.[12]

Scheme 1. Strategy for the Generation of *N*-Tosyl-3-azacyclohexyne



As depicted in Scheme 1, the formation of azacyclohexyne **1** via pathway a would involve a syn mode of elimination with triflate as leaving group. It did not escape our notice that the

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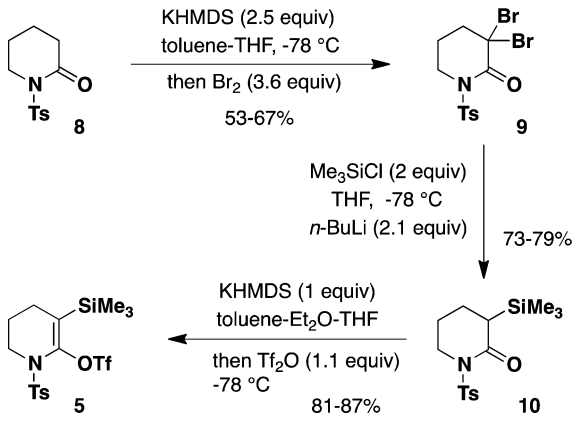
potential exists in this reaction for an alternative mode of fragmentation leading to alkynyl triflate **6** (pathway b). While it was our expectation that elimination of triflate would take precedence over anti elimination of the less electrofugal sulfonamide nitrogen, it occurred to us that **6** could itself undergo further reaction to afford the desired azacyclohexyne. Specifically, cyclization of **6** and α-elimination could produce the alkylidene carbene **7**, which could rearrange to azacyclohexyne as shown in Scheme 1. Note that the formation of alkylidene carbenes of type **7** via a closely related reaction of sulfonamide anions with alkynyliodonium salts has previously been reported by Feldman,[13] and the rearrangement of **7** to **1** finds precedent in the work of Wentrup depicted in eq 1.

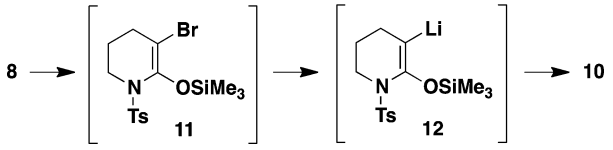
Scheme 2 outlines the synthesis of azacyclohexyne precursor **5** beginning with the readily available lactam **8**.[14] Direct C-

Scheme 2. Synthesis of Azacyclohexyne Precursor 5



silylation of **8** to afford **10** could not be achieved in good yield, so an alternative route was devised based on the sequence shown in Scheme 3. α-Bromination of lactam **8** followed by O-

Scheme 3. Strategy for α-Silylation of Lactam 8

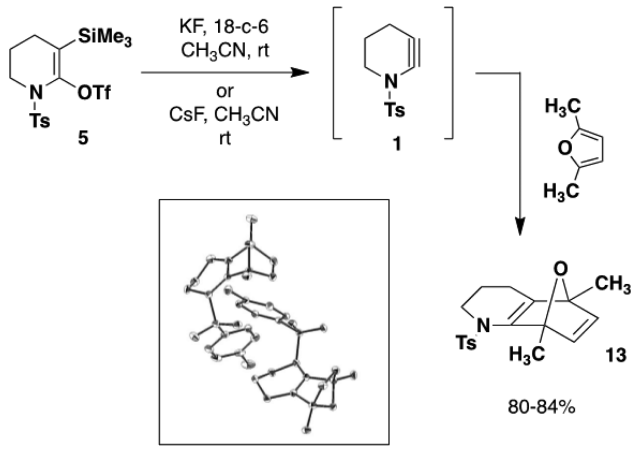


silylation of the α-bromo enolate was expected to provide **11**, and bromine–lithium exchange would then produce the vinyllithium intermediate **12** that was expected to undergo a 1,3 O to C silyl shift[15] to furnish **10** after aqueous workup. Alternatively, direct silylation of intermediate **12** at carbon followed by hydrolysis could also afford the desired α-silyl lactam.

In the event, monobromination of **8** could not be achieved cleanly, but the dibromide **9** could be obtained reproducibly and in good yield as a nicely crystalline solid after trituration. Conversion to α-silyl lactam **10** was then accomplished by addition of 1 equiv of BuLi to a solution of **9** and 2 equiv of Me_3SiCl in THF at −78 °C followed after 1 h by addition of a second equivalent of BuLi.[16] Deprotonation of **10** with 1 equiv of KHMDS and reaction of the resulting enolate with triflic anhydride then furnished the desired azacyclohexyne precursor **5** in good yield.

With an expeditious route to **5** in hand, we turned our attention to investigating the feasibility of employing this compound as a precursor to *N*-tosyl-3-azacyclohexyne. 2,5-Dimethylfuran was selected as a potential trap for the strained alkyne, and experiments were carried out by exposing the silyl triflate to the action of various fluoride reagents in the presence of 2 equiv of the furan. Tetrabutylammonium fluoride served as the fluoride source in our initial studies. Reaction of silyl triflate **5** (0.1 M in THF) with 2 equiv of Bu_4NF in the presence of dimethylfuran at 25 °C for 2 h led to the isolation in 60% yield of a white solid with spectroscopic data consistent with that expected for the product of Diels–Alder addition of the azacyclohexyne to dimethylfuran. Identification of the cycloadduct as **13** was established unequivocally by X-ray crystallographic analysis (Scheme 4).

Scheme 4. Generation and Trapping of *N*-Tosyl-3-azacyclohexyne



Further studies of this transformation revealed that **13** could be obtained in improved yield using 2 equiv of either cesium fluoride or KF/18-crown-6 as the fluoride source. Best results were obtained in reactions employing dilute solutions of **5** (0.05 M) in acetonitrile; for example, with KF/18-crown-6 the yield decreased from 80 to 68% when the concentration was increased from 0.05 to 0.15 M. No reaction took place with KF in the absence of 18-crown-6, and with CsF the yield was only 55% when 1.2 equiv rather than 2 equiv of the reagent was employed for the reaction.

The generation of *N*-tosyl-3-azacyclohexyne in the presence of various nucleophiles, electrophiles, and cycloaddition partners was examined next. Table 1 summarizes our results. [4 + 2] Cycloaddition of the strained heterocyclic alkyne with 2,3,4,5- tetraphenylcyclopentadienone ("tetracyclone") proceeded smoothly with spontaneous loss of CO by cycloreversion to afford the expected tetrahydroquinoline **14** in good yield.

The results of dipolar cycloadditions of the azacyclohexyne proved particularly interesting. Interception of **1** with benzyl azide[17] and with ethyl diazoacetate[18] took place with high regioselectivity to furnish a single cycloadduct in each case. Also completely regioselective was the reaction of the azacyclohexyne with 1,1,-diethoxyethylene[19] which gave **17** after brief exposure of the initial [2 + 2] cycloadduct to aqueous HCl.

Nucleophiles typically combine with arynes[2,20] and hetarynes[3] in good yield, and generation of the cyclic ynamide **1** in the presence of thiophenol afforded a single addition product

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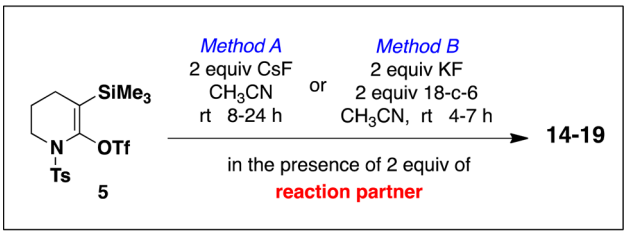
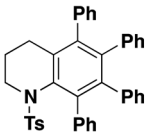
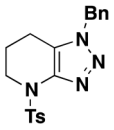
Table 1. Generation and Reactions of *N*-Tosyl-3-azacyclohexyne

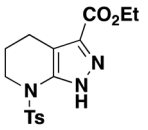




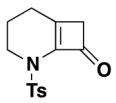
14 (83%)
Method A with
tetracyclone



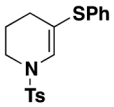
15 (63-71%)
Method B with
BnN_3



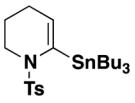
16 (75%)
Method A with
ethyl diazoacetate



17 (68%)
Method A with
$H_2C{=}C(OEt)_2$



18 (87%)
Method B with
PhSH



19 (75%)
Method A with
Bu_3SnH

18 in excellent yield.[21] A single product was also obtained when the azacyclohexyne was generated in the presence of tributyltin hydride.[22] In contrast to the efficient transformations presented in Table 1, several other reaction partners failed to afford trapping products in good yield. Complex mixtures were obtained when **1** was generated in the presence of 1,3-cyclohexadiene, the enolate derivatives of several 1,3-dicarbonyl compounds, 1-heptyne, and ethyl phenyl ketene.

Concerning the mechanism of the conversion of **5** to **1**, our observations to date are most consistent with the direct elimination pathway a shown in Scheme 1. Attempts to intercept an alkylidene carbene intermediate (**7**) by carrying out the reaction in cyclohexene or ethyl vinyl ether as solvent have not been successful, and no products have been detected from insertion of such a carbene on the aromatic ring of the tosyl group.[23]

The high level of regioselectivity observed in the reactions of *N*-tosyl-3-azacyclohexyne is especially noteworthy. The constraints imposed by the cyclic structure on the extent of interaction of the nitrogen lone pair with the highly distorted π bond suggest that reactions of **1** may follow a different course as compared to acyclic ynamides. Although Wentrup has reported IR evidence for the presence of a triple bond in 3-azacyclohexyne,[9] we consider it likely that **1** may exhibit significant zwitterionic character. We note that similar polarization of a strained heterocyclic triple bond has been invoked to account for the regiochemistry of additions to 1-thia-2-cyclooctyne.[24] By analogy, we propose that the regiochemical outcome of reactions of *N*-tosyl-3-azacyclohexyne can be predicted by a model in which the C-2 carbon of the azacyclohexyne manifests nucleophilic character and the C-3 carbon electrophilic character. Previously the regiochemistry of addition reactions of arynes[2] and hetarynes[3] has been rationalized by reference to frontier molecular orbital coefficients, substituent inductive effects, and the geometry interaction/distortion model introduced by Houk.[25] Computational studies are planned to provide a rigorous basis for understanding the chemistry of this fascinating heterocyclic alkyne.

In summary, the generation of *N*-tosyl-3-azacyclohexyne can be effected under mild conditions, and this strained heterocyclic alkyne engages in highly regioselective transformations with a variety of reaction partners providing access to nitrogen heterocyclic compounds that in many cases would not be easily obtained by alternative routes.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data (including X-ray crystallographic data for **13**), and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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